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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/571,882	BARNETT ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,26-28,30-35,38-41,43-46,50-57,60,61,63-73,79-82 and 84-90* is/are pending in the application.

4a) Of the above claim(s) *2,5,6,9,35,38-41,43-46,50-57,60,61,63-73,81 and 90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7,8,10-18,26-28,30-34,79,80,82 and 84-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 07 October 2009.

Claims 19-25, 29, 36, 37, 42, 47-49, 58, 59, 62, 74-78 and 83 have been cancelled.

Claims 1, 4-13, 16-18, 26-28, 30-35, 40, 41, 43-46, 50-52, 57, 60, 61, 66, 68, 71, 73, 79, 80 and 84-90 have been amended.

Claims 1-18, 26-28, 30-35, 38-41, 43-46, 50-57, 60, 61, 63-73, 79-82 and 84-90 are pending.

Claims 2, 5, 6, 9, 35, 38-41, 43-46, 50-57, 60, 61, 63-73, 81 and 90 are withdrawn.

Claims 1, 3, 4, 7, 8, 10-18, 26-28, 30-34, 79, 80, 82 and 84-89 are currently examined.

Claim Objections

The objection to claims 10, 12, 16, 27, 84 and 88 is withdrawn in response to Applicant's amendment.

Claim 82 is objected to because of the following informalities: it depends from claim 81, which has been withdrawn. Appropriate correction is required.

NEW REJECTION NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "a second polynucleotide sequence comprising a first coding sequence for a second HIV immunogenic polypeptide" in line 7 is confusing. The claim already recites "a first coding sequence for a first HIV immunogenic polypeptide" in lines 4-5. It is unclear how the "first coding sequence" is also for a second HIV immunogenic polypeptide.

WITHDRAWN REJECTIONS

The rejection of claims 18 and 26 under 35 U.S.C. §112, second paragraph, as being indefinite is withdrawn in response to the Applicants' amendment.

The rejection of claims 1, 3, 4, 7, 8, 10-12, 16, 27, 28, 32-34, 80, 82, 84, 88 and 89 under 35 U.S.C. §102(b) as being anticipated by Barnett *et al.* (1997) is withdrawn. Applicant's arguments, see page 20 in the bottom four lines, filed 07 October 2009, with respect to the rejections of claims 1, 3, 4, 7, 8, 10-12, 16, 27, 28, 32-34, 80, 82, 84, 88 and 89 under 35 U.S.C. 102(b) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combined teachings in the Barnett reference and the Aldovini patent as set forth below.

Applicant's arguments, see page 22 in the first paragraph, filed 7 October 2009, with respect to the rejection of claims 13-15 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection of claims 13-15 under 35 U.S.C. §103(a) as being obvious by Barnett *et al.* (1997) in view of Corbet *et al.* (2000) has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combined teachings in the Barnett reference, the Aldovini patent and the Corbet reference as set forth below.

Applicant's arguments, see page 22 in the first paragraph, filed 7 October 2009, with respect to the rejection of claims 30 and 31 under 35 U.S.C. 103(a) have been fully considered and are persuasive. Therefore, the rejection of claims 30 and 31 under 35 U.S.C. §103(a) as being obvious by Barnett *et al.* (1997) in view of Sailaja *et al.* (March 2003) has been withdrawn. However, upon further consideration, a new ground of rejection is made in view of the combined teachings in the Barnett reference, the Aldovini patent and the Sailaja reference as set forth below.

The rejection of claims 13, 17, 18, 85 and 86 under 35 U.S.C. §103(a) as being obvious by Barnett *et al.* (1997) in view of Aldovini *et al.* (US 5,861,282) and Surman *et al.* (2001) is withdrawn in light of the new ground of rejection below.

NEW REJECTIONS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments with respect to claims 1, 3, 4, 7, 8, 10-13, 16-18, 27, 28, 32-34, 79, 80, 82, 84-86, 88 and 89 have been considered but are moot in view of the new ground of rejection.

Claims 1, 3, 4, 7, 8, 10-13, 16-18, 27, 28, 32-34, 79, 80, 82, 84-86, 88 and 89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (1997, hereinafter "Barnett") in view of Aldovini *et al.* (US 5,861, 282, 19 January 1999).

Claims 1, 27, 28 and 80 are directed to a composition comprising a polynucleotide component encoding a first HIV immunogen of a first strain and a polypeptide component comprising a second HIV immunogen of a second strain, the first HIV immunogen is analogous but is of a different strain than the second HIV immunogen. Claims 3 and 82 further limit the first and second strains to be of different subtypes. Claim 12 further limits the components to be native. Claim 13 further limits the polynucleotide component to be synthetic. Claim 16 further limits the first and second HIV immunogens to be HIV envelope polypeptides. Claims 17, 18, 85 and 86 further limit the first or second HIV immunogenic polypeptide to comprise an alteration or mutation such as a mutation in the cleavage site or a mutation in the V1, V2, or V3 region. Claims 32-34 further limit the polynucleotide component to comprise a control element, specifically a CMV promoter. Claim 79 further limits the polypeptide component to be expressed on a virus like particle.

Claims 4, 88 and 89 are directed to a composition comprising a polynucleotide component to comprising a first and second polynucleotide sequences encoding analogous HIV immunogens but of different strains and a polypeptide comprising a third HIV immunogen, and if the polypeptide component comprises two or more HIV immunogenic polypeptides, then at least one of the two or more HIV immunogens is derived from a different HIV strain than the first and second HIV immunogens encoded by the polynucleotide component. Claim 7 further limits the first and second polynucleotide sequences to be of different subtypes. Claim 8 further limits the third HIV immunogen to be of a different subtype than the first and second HIV immunogens. Claim 10 limits the first and third HIV immunogen to be of different strains. Claim 11 further limits the first and third HIV immunogen to be of different subtypes. Claims 84 further limits the first and second HIV immunogens to be HIV envelope polypeptides.

Barnett discloses immunization with a polynucleotide component containing a plasmid comprising a CMV promoter and DNA sequences for HIV envelope protein, gp120, from strains CM235 (Thai subtype E) and US4 (North American subtype B) and then boosting with a polypeptide component comprising a recombinant subunit protein of HIV-1 gp120 from strains CM235 and SF2. See page 869, right column, in the section with the title: HIV gp120 plasmids and recombinant gp120 protein.

Barnett does not explicitly disclose combining the plasmids with the recombinant subunit protein into a composition.

However, Aldovini discloses compositions prepared by combining HIV particles containing a spectrum of various Env proteins for wider protection and for more specific or general detection of various strains of HIV (column 8, lines 47-52). The compositions for vaccination purposes can be delivered in an appropriate physiological carrier, such as saline. The carrier can contain an adjuvant (column 10, lines 39-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV gp120 plasmids (polynucleotide component) and the gp120 protein subunits (the polypeptide component) of Barnett so as to combine them into a composition for immunization and to express the polypeptide component on virus like particles for better presentation of the HIV envelope peptide. One having ordinary skill in the art would have been motivated to combine the polynucleotides and the polypeptides, each performing the same immunogenic function, into one composition for the same functional purpose, to improve the efficiency of the immunization with the predictable results of generating an immune response. There would have been a reasonable expectation of success, given that VLP is a vehicle for protein expression known in the art, as taught by Aldovini.

Barnet does not disclose an alteration or mutation in the first or second HIV Env polypeptide, such as a mutation in the cleavage site or a mutation in the glycosylation site.

However, Aldovini suggests alterations in a HIV nucleotide sequence and non-infectious immunogenic HIV particles (Abstract). Specifically, Aldovini suggests mutations or deletions in the gp160 cleavage site to retain the gp120 antigen, which blocks the processing of the gp160 envelope precursor to gp120 and gp41 and reduces

the "shedding" of gp120 antigen. The HIV Env variable regions (V1, V2, V3) can be modified by replacing the native gene with a variant gene from another HIV strain or isolate in order to tailor the resulting non-infectious HIV particles to immunize against HIV strains which are prevalent in a population or against particularly virulent strains. See column 8, lines 1-60.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the native sequences of HIV-1 immunogenic polypeptides of Barnett into synthetic polynucleotides by altering or mutating the cleavage site and/or the variable regions. One having ordinary skill in the art would have been motivated to alter and mutate the HIV Env sequence to improve antigenic or immunogenic properties and for obtaining HIV diagnostic reagents that are more specific or more general in detecting various strains of HIV, as per the suggestion by Aldovini.

Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 13-15 have been considered but are moot in view of the new ground of rejection.

Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (1997, hereinafter “Barnett”) in view of Aldovini *et al.* (US 5,861, 282, 19 January 1999) and Corbet *et al.* (2000, hereinafter “Corbet”).

Claims 13-15 further limit the polynucleotide component to codons optimized for expression in mammalian and human cells.

The relevance of Barnett and Aldovini is set forth above. Barnet and Aldovini do not disclose codon optimization.

Corbet suggests codon-optimized HIV-1 envelope genes by removal of the internalization signals and the exchange of the highly biased AT-rich HIV codon usage with that of highly expressed GC-rich human genes, which renders the envelope expression Rev-independent and improves the expression of the humanized HIV envelope protein in mammalian cell lines. See Abstract and pages 1997-1998, Introduction. Corbet specifically discloses the benefit of increased specific cellular and humoral immune response. See page 2002, right column.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV-1 Env gp120 coding polynucleotides of Banett so as to optimize the codons in the polynucleotide sequences as suggested by Corbet. One having ordinary skill in the art would have been motivated to make such a modification to improve the expression of the HIV antigens in order to enhance the immune responses as per Corbet's suggestion. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claims 30 and 31 have been considered but are moot in view of the new ground of rejection.

Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnett *et al.* (1997, hereinafter "Barnett") in view of Aldovini *et al.* (US 5,861, 282, 19 January 1999) and Sailaja *et al.* (March 2003, hereinafter "Sailaja").

Claims 30 and 31 further limit the invention to comprising an additional antigenic polynucleotide or polypeptide that is not derived from an HIV-1 strain.

The relevance of Barnett and Aldovini is set forth above. Barnet and Aldovini do not disclose an additional antigenic polynucleotide or polypeptide that is not derived from an HIV-1 strain.

Sailaja suggests adding a polypeptide antigen, the extracellular domain of Fms-like tyrosine kinase receptor-3 ligand (FLex), or the DNA encoding FLex, to the HIV-1 Env, in order to obtain long-term maintenance of gp120-specific immune responses through dendritic cell expansion. See page 2497, left column, first two paragraphs.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine or fuse the HIV *env* polynucleotide or Env polypeptide of Barnett with the FLex polypeptide or FLex coding sequence of Sailaja so as to augment the HIV Env immune response as suggested by Sailaja. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

MAINTAINED REJECTION

The rejection of claims 26 and 87 under 35 U.S.C. §103(a) as being obvious over Barnett *et al.* (1997, hereinafter "Barnett") in view of Aldovini *et al.* (US 5,861, 282, 19 January 1999) and Surman *et al.* (2001, hereinafter "Surman) is maintained.

Claims 26 and 87 further limit the HIV Env polypeptide to contain a mutation that exposes a neutralizing epitope of the HIV Env, specifically, a CD4 binding region or an envelope binding region that binds to a CCR5 chemokine co-receptor.

The relevance of Barnett is set forth above. Barnett does not disclose alteration or mutation in the HIV immunogenic polypeptides.

Aldovini suggests removing Env glycosylation sites to improve antigenic or immunogenic properties. See column 8, lines 52-56.

Aldovini does not explicitly disclose the benefit of deleting glycosylation sites in HIV Env, which is the exposure of CD4 or coreceptor binding sites. However, Surman discloses that the epitopes of CD4 binding regions are heavily bordered by glycosylation sties. See Abstract and page 4590, right column, last paragraph. Therefore, removal of the glycosylation sites renders strings of epitopes that are only the CD4 binding regions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV Env immunogenic polypeptides of Banett so as to mutate the HIV Env sequence by deleting the glycosylation sites, which results in the exposing a CD4 binding region. One having ordinary skill in the art would have been motivated to make such a modification to improve the antigenic or immunogenic properties as per Aldovini's suggestion. There would have been a reasonable expectation of success, given the heavy glycosylation in the epitope regions as disclosed by Surman. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that Barnett does not teach or suggest a single composition containing both a polynucleotide component encoding an HIV immunogenic peptide and an

analogous HIV immunogenic polypeptide. None of Aldovini, Surman, Corbet, or Sailaja teaches or suggests including both of these components in a single composition.

A step in the obviousness analysis is to "determine whether there was an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398,418 (2007). In the instant case, it is *prima facie* obvious to combine two antigenic components (the plasmid and the recombinant HIV protein) disclosed in the Barnett reference to form a composition to be used for HIV immunization. See MPEP 2144.06 [R-6] Art Recognized Equivalent for the Same Purpose>I.< Combining Equivalents Known for the Same Purpose. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992).

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir.

1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claim is allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648